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Optimal Effect-Site Concentration of Remifentanil for Inhibiting Response to Laryngeal Mask Airway Removal during Emergence

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Purpose: This randomized, controlled, double-blind study was designed to determine the optimal dose of remifentanil for preventing complications associated with the removal of a laryngeal mask airway (LMA) without delaying emergence. **Materials and Methods:** This study randomly assigned 128 patients to remifentanil effect-site concentrations (Ce) of 0 ng/mL (group R0), 0.5 ng/mL (group R0.5), 1.0 ng/mL (group R1.0), and 1.5 ng/mL (group R1.5) during emergence. The emergence and recovery profiles were recorded. Adverse events such as coughing, airway obstruction, breath-holding, agitation, desaturation, nausea, and vomiting were also evaluated. **Results:** The number of patients with respiratory complications such as coughing and breath-holding was significantly lower in the R1.0 and R1.5 groups than in the R0 group (p<0.05). Emergence agitation also decreased in the R1.0 and R1.5 groups (p<0.0083). The time to LMA removal was significantly longer in the R1.5 group than in the other groups (p<0.05). **Conclusion:** Maintaining a remifentanil Ce of 1.0 ng/mL during emergence may suppress adverse events such as coughing, breath-holding, and agitation following the removal of LMA without delayed awakening.

Key Words: Emergence, laryngeal mask airway, remifentanil

INTRODUCTION

The laryngeal mask airway (LMA) should be removed when the patient is completely awake.[1] However, complications such as coughing or airway obstruction may accompany LMA removal after the return of airway reflexes.[2,3] Remifentanil has recently been shown to suppress the airway reflex and facilitate smooth extubation during recovery from general anesthesia.[4,5] Therefore, smooth LMA removal may be possible even in the awake state by using remifentanil. Remifentanil, however, also has the risk of delayed awakening.[5]

This randomized, controlled, double-blind study was designed to assess the effects of four effect-site concentrations (Ce) of remifentanil via target-controlled infusion (TCI) to determine the optimal dose for preventing complications associated with LMA removal without delaying emergence after sevoflurane-remifentanil anesthesia.

MATERIALS AND METHODS

Institutional Review Board approval was obtained for this study, and written informed consent was additionally obtained from patients (ASA physical status 1–2, ages 18–65 years) undergoing arthroscopic knee surgery (e.g., meniscus repair, reconstruction of the anterior cruciate ligament) under general anesthesia. The exclusion criteria included potentially difficult airways (cervical spine disease, Mallampati classification 3 or 4, or mouth opening <2.5 cm), asthma, chronic obstructive pulmonary disease, signs of upper respiratory infection, risk of gastric aspiration, or obesity (body mass index >30 kg/m^2). We also excluded patients with psychological or emotional disorders, abnormal cognitive development, developmental delay, or a known history of allergy to the drugs in our protocol. Patients were randomly assigned to one of four groups according to a computer-generated random table. All patients received a predetermined Ce of remifentanil by TCI according to their group assignments 10 minutes before the end of surgery (R0: 0 ng/mL; R0.5: 0.5 ng/mL; R1.0: 1.0 ng/mL; R1.5: 1.5 ng/mL). A TCI pump (Orchestra Module DPS, Fresenius-Vial, Brezins, France) using Minto's pharmacokinetic model was used for effect-site target-controlled infusion of remifentanil.

All patients were premedicated with intravenous glycopyrrolate 0.2 mg immediately prior to induction of anesthesia. Electrocardiogram, noninvasive blood pressure, peripheral oxygen saturation, end-tidal CO_2, inhaled and exhaled end-tidal sevoflurane concentrations, and bispectral index were monitored. Anesthesia was induced with intravenous propofol 1.5 mg/kg, a remifentanil Ce of 3 ng/mL via TCI, and 2 vol% sevoflurane. A classic LMA was inserted 5 minutes after remifentanil infusion. The size of the LMA was determined according to the manufacturer's guidelines, which proposes size 3 for 30–50 kg, 4 for 50–70 kg, and 5 for 70–100 kg. Anesthesia was maintained using sevoflurane and remifentanil supplemented with 50% oxygen and air 3 L/min. The tidal volume was set at 8 mL/kg, and the respiratory rate was adjusted to maintain $EtCO_2$ at 35–40 mm Hg.

Two anesthetists participated in the emergence phase. The first practitioner knew the group assignment of each patient, whereas the second practitioner did not. An operator was asked to provide a warning 10 minutes before the end of surgery, at which time the first practitioner covered the TCI pump with foil and adjusted the Ce of remifentanil according to the group assignment. Sevoflurane was also set to 1.5 vol%. After the completion of wound dressing, sevoflurane was stopped, and mechanical ventilation was maintained with 100% oxygen at 8 mL/kg. The respiratory rate was maintained at 10 breaths/min by the first practitioner. Patients were given the verbal request to open their eyes, with smooth tactile stimulation at 10-second intervals. When the patient awoke, the LMA was removed without the deflation of the cuff. An awake state was defined as the recovery of consciousness and the ability to respond to verbal commands. Remifentanil infusion was stopped after LMA removal. The patient was moved to a post anesthesia care unit (PACU) when adequate spontaneous respiration was confirmed for 5 more minutes.

The second anesthetist, who was blinded to the Ce of remifentanil, recorded the following variables. Mean arterial pressure (MAP), heart rate (HR), SpO_2, and end-tidal sevoflurane concentration were recorded upon entry into the operation room (T0), 2 minutes after the end of surgery (T4), immediately prior to the removal of the LMA (T5), 2 minutes after LMA removal (T6), and 10 minutes after arrival in the PACU (T7). Airway complications (airway obstruction, desaturation to SpO_2 <94%, breath holding, and coughing), nausea, vomiting, and the Riker sedation-agitation scale[6] were assessed during the emergence phase. The Riker sedation-agitation scale was rated on a seven-point scale: 1=unable to rouse; 2=very sedated; 3=sedated; 4=calm and cooperative; 5=agitated; 6=very agitated; 7=dangerous agitation.[6] A score closer to 4 indicated that a patient was calmer, more easily awakened, and better at following commands. Desaturation, nausea, and vomiting were also recorded during the PACU stay. The observer's assessment of alertness/sedation (OAA/S) scale and numerical rating scale for pain (0, no pain; 10, worst possible pain) were also measured 10 minutes after arrival in the PACU. The OAA/S assessment for the evaluation of the sedation level was based on response to name spoken or shaking, speech, facial expression, and eyes (clear or ptosis).[7] Maximun score was 20 and score closer to 20 indicated that a patient was alert. Airway obstruction was defined as stridor, tracheal tug, or paradoxical chest and abdominal movement. Breath-holding was defined as apnea lasting more than 20 seconds. The grade of coughing was assessed using a 4-point scale in which 0 indicates no coughing, 1 indicates a single coughing episode, 2 indicates more than one episode of non-sustained coughing, and 3 indicates sustained and repetitive coughing with head tilt. Severe coughing was assessed as

either grade 2 or 3. The emergence phase was defined as the period from the end of surgery until arrival in the PACU. The duration of anesthesia, LMA removal time (duration between the end of surgery and LMA removal), and PACU discharge time were also recorded. The PACU discharge time was the period from arrival in the PACU until the attainment of a modified Aldrete's score of at least 9.[8]

The primary end point was the incidence of airway complications during emergence. The secondary end points were the LMA removal time, the PACU discharge time, the Riker sedation-agitation scale, the OAA/S scale, the numerical rating scale for pain, and the incidence of nausea and vomiting.

The incidence of respiratory complications during LMA removal in awake patients has been reported as 48.7%.[3] A minimum sample size of 26 patients per group was required to achieve a power of 0.8 and an α value of 0.05 on the assumption that a 50% reduction of complications would be clinically significant. Statistical analysis was performed with SPSS 21.0 (IBM, Armonk, NY, USA). Data were presented as number, mean (SD), or median (range) as appropriate. Normally distributed continuous data were analyzed using a one way analysis of variance (ANOVA). Continuous variables that were non-normally distributed were analyzed with the Kruskal-Wallis test. Repeated measure ANOVA with Bonferroni's post-hoc testing was employed for HR and MAP. Categorical data such as sex, airway complications, coughing, breath holding, airway obstructions, desaturation, nausea, and vomiting were analyzed using a chi-squared test. When the variables were not independent in the chi-squired tests, comparisons of column proportions (Z-tests) with Bonferroni's correction were performed to see which rows and columns were responsible for this relationship. The Riker sedation-agitation scale was analyzed with the Kruskal-Wallis test, and post-hoc analysis was performed using the Mann-Whitney U test with the p-value adjusted with Bonferroni's correction ($p<0.0083$). $p<0.05$ was considered statistically significant; however, $p<0.0083$ was considered to be the limit of statistical significance in the Riker sedation-agitation scale.

RESULTS

Of the 128 patients enrolled in this study, 120 completed the study. Eight patients were excluded from the study for the following reasons: failure to insert the LMA (2 in R0, 1 in R0.5, 1 in R1.0, 1 in R1.5) and failure to maintain adequate ventilation after the insertion of the LMA (2 in R0.5, 1 in R1.5) (Fig. 1). No differences were found among the groups when regarding patient characteristics (Table 1). Operative characteristics (operation time, anesthesia time, end-tidal sevoflurane concentration at LMA removal, and total dose of remifentanil) were also similar among the groups (Table 1).

In the R1.5 group, HR at emergence (2 minutes after LMA removal) was significantly lower than in the control group

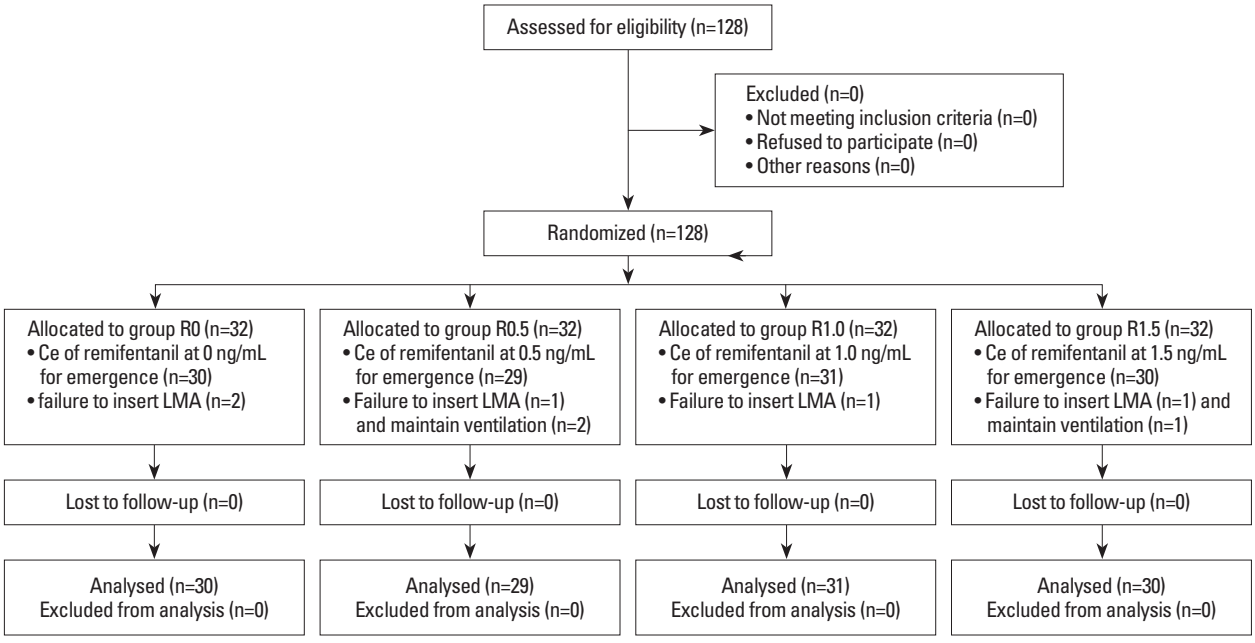

Fig. 1. CONSORT diagram. Ce, effect-site concentration; LMA, laryngeal mask airway.

Table 1. Patient and Operative Characteristics

	Group R0 (n=30)	Group R0.5 (n=29)	Group R1.0 (n=31)	Group R1.5 (n=30)
Age (yrs)	40.23±14.07	37.24±14.57	38.55±16.37	34.33±14.39
Sex (male/female)	16/14	12/17	15/16	15/15
Weight (kg)	67.77±13.74	64.72±10.35	66.52±10.02	69.87±10.58
Height (cm)	166.60±9.15	167.79±9.23	169.16±8.78	171.07±6.11
Smoker (n)	6	7	8	6
Operation time (min)	75.33±46.16	57.59±30.43	60.97±40.77	63.67±38.17
Anesthesia time (min)	111.67±50.73	97.07±31.75	92.26±47.78	100.33±46.16
Total dose of remifentanil (μg)	555.97±363.98	536.90±270.47	499.77±334.17	560.40±261.41
EtSe at T5 (vol%)	0.20±0.08	0.16±0.07	0.18±0.07	0.18±0.07

EtSe at T5, end-tidal sevoflurane concentration immediately prior to removal of the laryngeal mask airway; R0, Ce of remifentanil at 0 ng/mL; R0.5, Ce of remifentanil at 0.5 ng/mL; R1.0, Ce of remifentanil at 1.0 ng/mL; R1.5, Ce of remifentanil at 1.5 ng/mL during emergence. Values are mean±SD or number of patients. There are no significant differences among the groups.

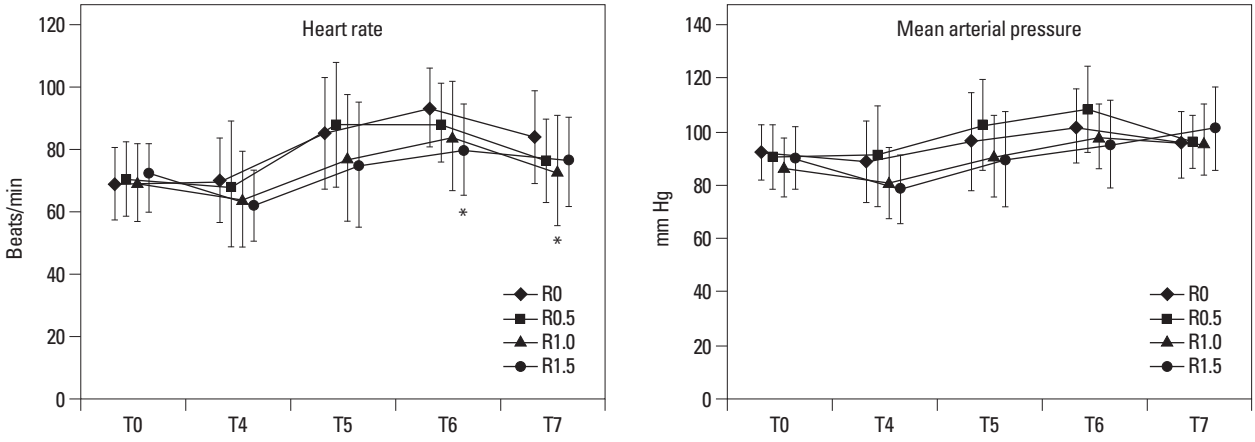

Fig. 2. Changes in heart rate and mean arterial pressure during emergence. Data are expressed mean±SD. T0, entry into the operation room; T4, 2 minutes after the end of the surgery; T5, immediately prior to removal of the laryngeal mask airway; T6, 2 minutes after removal; T7, 10 minutes after arrival in the PACU. *p<0.05, compared to R0 group. PACU, post anesthesia care unit.

(R0 group) (Fig. 2). HR was also significantly lower in the R1.0 group than in the R0 group after arrival in the PACU (Fig. 2). There were no differences in the MAP among the groups (Fig. 2). The total number of patients with airway complications (coughing, breath-holding, airway obstruction, or desaturation) during emergence was significantly lower in the R1.0 and R1.5 groups than in the R0 group (p< 0.05) (Table 2). There were also differences in the incidence of breath holding and coughing, as well as in the severity of coughing grade, among the airway complications. The incidence of coughing and the severity of coughing grade were lower in R1.0 and R1.5 groups than in the R0 group (p<0.05) (Table 2). The incidence of breath holding was significantly lower in the R1.0 group than in the R0 group (p<0.05) (Table 2). The time to LMA removal was significantly longer in the R1.5 group than in the other groups (p<0.05) (Table 2). During emergence, the Riker sedation-agitation scale was closer to 4 (calm and cooperative state) in the R1.0 and R1.5 groups than in the R0 group (p<0.0083) (Table 2). There were no differences in the incidence of postoperative nausea and vomiting, OAA/S score and numeric rating scale in the PACU, and PACU discharge time between the four groups (Table 3).

DISCUSSION

This study showed that maintaining remifentanil infusion at a Ce of 1.0 ng/mL during emergence reduced adverse responses to LMA removal, including respiratory complications, compared with other groups and without delayed emergence.

Intravenous opioids have been reported to suppress responses to airway irritation.[9] Continuous infusion of a remifentanil Ce of 1.5 ng/mL during emergence reduced the incidence and severity of coughing when using a tracheal tube.[4,5] In our study, we decided to use doses under 1.5 ng/mL as an LMA is less irritable to the airway than a tracheal tube.[10]

Table 2. Complications during Emergence

	Group R0 (n=30)	Group R0.5 (n=29)	Group R1.0 (n=31)	Group R1.5 (n=30)
Time to LMA removal (sec)	295.07±123.24	357.14±126.33	321.84±96.52	500.63±192.01*
N of Pt with airway Cx (n)	19	17	4†	6†
Coughing (n)	10	7	1†	0†
Grade 1	0	2	0	0
Grade ≥2	10	5	1†	0†
Breath holding (n)	13	14	3†	6
Airway obstruction (n)	1	0	0	1
Desaturation (n)	0	0	0	0
RAS scale	5 (4–7)	5 (4–6)	4 (4–6)‡	4 (4–6)‡

N, number; Pt, patients; Cx, complication; RAS, Riker sedation-agitation scale; Ce, effect-site concentration; LMA, laryngeal mask airway.
Values are mean±SD, number, or median (range). R0, Ce of remifentanil at 0 ng/mL; R0.5, Ce of remifentanil at 0.5 ng/mL; R1.0, Ce of remifentanil at 1.0 ng/mL; R1.5, Ce of remifentanil at 1.5 ng/mL during emergence.
*p<0.05 versus the other groups.
†p<0.05 versus the group R0.
‡p<0.0083 versus the group R0 (p-value was collected with Bonferroni's method).

Table 3. Data from PACU, Postoperative Nausea and Vomiting

	Group R0 (n=30)	Group R0.5 (n=29)	Group R1.0 (n=31)	Group R1.5 (n=30)
Time of PACU discharge (min)	13.00±2.49	14.31±2.90	14.35±2.81	14.17±1.90
Nausea and vomiting (n)	2	0	3	2
OAA/S (score)	19.63±1.13	19.41±0.98	19.61±1.26	19.71±1.68
NRS (score)	6.00±1.29	5.28±1.91	5.39±1.93	5.17±2.09

PACU, postanesthetic care unit; OAA/S, Observer's Assessment of Alertness/Sedation scale; NRS, numerical rating scale; Ce, effect-site concentration.
Values are mean±SD or number. There are no significant differences among the groups. R0, Ce of remifentanil at 0 ng/mL; R0.5, Ce of remifentanil at 0.5 ng/mL; R1.0, Ce of remifentanil at 1.0 ng/mL; R1.5, Ce of remifentanil at 1.5 ng/mL during emergence.

The results showed that the incidence of respiratory problems was 63.3% in the control group (the R0 group), yet less than 20% in the groups maintaining a remifentanil Ce of 1.0 and 1.5 ng/mL.

Baird, et al.[3] reported that desaturation and airway obstruction following the LMA removal after full recovery occurred in 31% and 7% of adult patients, respectively. On the other hand, several previous studies on adults reported that the occurrence of such major complications was rare during LMA removal in the awake state.[11,12] Despite the high incidence of respiratory complications in our study (63%), major respiratory problems were also very rare (2 out of a total of 120 adult patients), and there were no significant differences among the groups. We found that remifentanil did not reduce these major problems during LMA removal. The difference in the incidences of major respiratory complications among these studies may be due to different methodologies or criteria used to investigate major respiratory complications. Therefore, it is difficult to conclude whether the use of an LMA is relevant to major respiratory complications. Further research is warranted to study the incidence of major respiratory complications following LMA removal and to determine whether these complications can be prevented by remifentanil.

Minor problems such as coughing may lead to many dangerous effects, including laryngospasm, bleeding in the surgical field, and harmful hemodynamic changes. Therefore, preventing minor problems following LMA removal may be no less important than preventing major complications such as airway obstructions. Several studies have tried to prevent coughing during emergence.[4,5] In our study, maintaining a remifentanil Ce of 1.0 or 1.5 ng/mL during emergence reduced the incidence of coughing, and severe coughing episodes also decreased. The reason for the reduction of these complications may be that remifentanil provides good tolerance for the LMA.

Delayed emergence and respiratory depression place limitations on the use of opioids during recovery. If the dose is titrated well, however, remifentanil can minimize these adverse events during emergence due to its very short duration of action.[13] A previous study demonstrated that a remifentanil Ce of 1.5 ng/mL was an effective dose for blunting airway responses to tracheal extubation without the risks of delayed emergence and hypoventilation.[4] In contrast to that

study, Jun, et al.[5] reported a delayed awakening and reduced respiratory rate with a remifentanil Ce of 1.5 ng/mL when compared with groups in which remifentanil was stopped or set at a Ce of 1.0 ng/mL. Our study also showed that a remifentanil Ce of 1.5 ng/mL resulted in a longer time to LMA removal than in the control group, whereas a remifentanil Ce of 1.0 ng/mL did not. Therefore, a remifentanil Ce of 1.0 ng/mL can be considered safe in terms of avoiding delayed emergence or hypoventilation during LMA removal.

Opioids can lead to postoperative nausea and vomiting (PONV) through diverse mechanisms; however, we did not find any differences in the incidence of PONV. Likewise, in previous studies, no significant differences in the incidence of PONV were found between groups each receiving a remifentanil Ce of below 1.5 ng/mL.[4,5,12] This result may be attributable to the rapid systemic elimination of remifentanil. In a study on the incidence of PONV caused by opioids with different durations of action, remifentanil reduced the incidence of PONV compared with fentanyl, a longer-acting opioid.[14]

The use of opioids during recovery from general anesthesia can decrease agitation.[15] In our study, emergence agitation decreased at remifentanil concentrations of 1.0 and 1.5 ng/mL. Remifentanil provides good tolerance of tracheal tubes and LMAs, and it may be the cause of the observed reduction in emergence agitation.

A limitation of this study is that there was no treatment of postoperative pain. The stimulation by the LMA was similar in all patients; however, the pain degree of each patient caused by surgical stimuli might have been different due to the kind of surgery and operative time. Therefore, the level of postoperative pain may have an influence on adverse events such as emergence agitation.

In conclusion, maintaining a remifentanil Ce of 1.0 ng/mL during emergence may suppress adverse events such as coughing, breath holding, and agitation following LMA removal without delayed awakening.

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